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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/151,409	09/10/1998	JAMES B. DALE	481112.410	7693

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EXAMINER	
DEVI, SARVAMANGALA J N	

ART UNIT	PAPER NUMBER
1645	35

DATE MAILED: 01/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applic[illegible]s)
09/151,409	Dale
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 17, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *12, 15-17, 19, 21, 23, 27, 30-32, 36-38, 40, 42, 44, and 54-58* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *12, 15-17, 19, 21, 23, 27, 30-32, 36-38, 40, 42, 44, and 54-58* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Oct 17, 2002* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

RESPONSE TO APPLICANT'S AMENDMENT

Applicant's Amendment

1) Acknowledgment is made of Applicant's amendment filed 10/17/02 (paper no. 33) in response to the non-final Office Action mailed 07/26/02 (paper no. 32), which amendment has been entered. With this, Applicant has amended the specification.

Status of Claims

2) Claims 12, 16, 27, 37 and 56 have been amended via the amendment filed 10/17/02.

Claims 12, 15-17, 19, 21, 23, 27, 30-32, 34, 36-38, 40, 42, 44 and 54-58 are pending and are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Specification

5) The amendment introduced to the paragraph beginning at line 17 of page 3 replaces the recitation "90.3%" with "86% to 89%". Applicant does not provide any justification for the amendment, or point to a specific part of the specification as originally filed that supports this amendment. This amendment to the specification is objected to under 35 U.S.C. § 132 because it introduces new matter into the disclosure. 35 U.S.C. § 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: "86% to 89%". Applicant is required to cancel the new matter in the response to this Office Action.

Objection(s) Withdrawn

6) The objection to the drawings made in paragraph 1 of the Office Action mailed 05/26/99 (paper no. 11) is withdrawn in light of the formal drawings filed 10/17/02 (paper no. 33) which have been approved by the Draftsperson.

Rejection(s) Withdrawn

7) The rejection of claims 12, 15, 17, 19, 21, 23, 27, 30-32, 34, 36, 38, 40, 42, 44, 54, 55, 57 and 58 made in paragraph 11 of the Office Action mailed 07/26/02 (paper no. 32) under 35 U.S.C. § 112, first paragraph, as being non-enabled with regard to the scope, is withdrawn in light of Applicant's amendments to the claims and/or the base claim(s).

8) The rejection of claims 16, 37 and 56 made in paragraph 12(a) of the Office Action mailed 07/26/02 (paper no. 32) under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendments to the claims and/or the base claim(s).

9) The rejection of claim 57 made in paragraph 12(b) of the Office Action mailed 07/26/02 (paper no. 32) under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendments to the claim and/or the base claim.

10) The rejection of claims 12, 15, 27 and 36 made in paragraph 13 of the Office Action mailed 07/26/02 (paper no. 32) under 35 U.S.C. § 103(a) as being unpatentable over Hruby *et al.* (*PNAS* 88: 3190-3194, 1991) in view of Marston *et al.* (*In*: *Methods in Enzymology, Guide to Protein Purification*. (Ed) MP Deutscher. vol. 182, section 20, pages 264-276), is withdrawn for reasons explained herebelow.

Response to Applicant's Arguments on the Art Rejection

11) Applicant contends that the present invention is directed to a recombinant fusion polypeptide comprising: a) multivalent immunogenic portion which comprises at least two immunogenic polypeptides from group A streptococcal M protein comprising at least ten amino acids and capable of eliciting an immune response against group A *Streptococci*; b) a carboxy-terminal polypeptide which is a reiteration of at least one immunogenic polypeptide from the amino-terminal of the immunogenic portion. Applicant alleges that a *prima facie* case of obviousness has not been established by the Office because neither Hruby *et al.* nor Marston *et al.* individually or in combination teach or suggest every limitation of the instant claims. Applicant submits that the references fail to teach or suggest a fusion polypeptide comprising a "multivalent" immunogenic portion having at least two immunogenic polypeptides and a carboxy-terminal polypeptide that is a "reiteration" of at least one immunogenic polypeptide from the amino terminal of the immunogenic portion. Applicant acknowledges that Hruby *et al.* teach the construction of tandem in-frame

"repeats" of the C-repeat region (CRR) from Group A streptococcal M6 protein imbedded in and fused to the thymidine kinase (TK) of vaccinia virus. Applicant asserts that Hruby's 3-copy CRR tandem repeat has fused at the carboxyl terminus a portion of the vaccinia virus TK gene and is expressed as a fusion having the structure [CRR]n-TK. Applicant therefore contends that the carboxy-terminal polypeptide is not a reiteration of an immunogenic polypeptide from the immunogenic portion. Applicant cites case law and alleges that the Office has failed to articulate what portions of Marston and Hartley and Hruby *et al.* provide the motivation or suggestion to combine the references.

Applicant's arguments have been carefully considered, but are not persuasive. As explained below under the art rejection, instant claims are broad and use the open claim language, and therefore read on the cited art. As Applicant acknowledges, Hruby's 3-copy CRR tandem repeat of Group A streptococcal M6 protein, fused to a portion of the vaccinia virus TK gene at the carboxyl terminus and expressed as a fusion having the structure [CRR]n-TK, meets the structural elements recited in parts (a) and (b) of the base claims. The Hruby's 3-copy CRR tandem repeat serves as the instantly recited immunogenic portion since it 'comprises' at least two polypeptides that are at least ten amino acids, and the third CRR repeat, being a reiteration of the earlier CRR repeat, serves as the carboxy-terminal polypeptide of the immunogenic portion. Since this entire 3-copy CRR tandem repeat portion is expressed as a fusion with thymidine kinase (TK)of vaccinia virus, it meets the instantly claimed recombinant fusion polypeptide. Because of the open claim language used in the instant base claims, Hruby's thymidine kinase fusion element can be present either at the carboxy or amino-terminal of the immunogenic portion comprising the 3-copy CRR tandem repeat. Hruby's 3-copy CRR tandem repeat portion also serves intrinsically as a multivalent immunogenic portion, because CRRs were known in the art to be shared among heterologous serotypes of Group A streptococci. Solely for the reason that Mori *et al.* (see below) provide the structural composition of the three at least 10 amino-acid long fragments of the Group A streptococcal M protein present in the multivalent immunogenic portion of the claimed recombinant fusion polypeptide and therefore better demonstrate the non-novel nature of the broadly recited claims 12, 15, 27 and 36, the Hruby reference is withdrawn. An art rejection is made below using Mori's reference to show how the breadth of claims 12, 15, 27 and 36 and the open claim language used in these claims render these

claims not novel.

Rejection(s) under 35 U.S.C. § 102

12) Claims 12, 15, 27 and 36 are rejected under 35 U.S.C. § 102(b) as being anticipated by Mori *et al.* (*Pediatr. Res.* 39: 336-342, February 1996) as evidenced by Fischetti *et al.* (US 5,985,654) or Vashishstha *et al.* (*J. Immunol.* 150: 4693-4701, May 1993, already of record).

It is noted that the recitation 'at least 10 amino acids' encompasses both contiguous and non-contiguous amino acids. The term 'at least two immunogenic polypeptides' is not limited to immunogenic polypeptides from the amino terminal portion of a Group A streptococcal M protein.

Instant claims include the open claim language, such as, fusion polypeptide "comprising"; immunogenic portion "comprises"; and polypeptides 'comprising' at least 10 amino acids. The transitional limitations "having" or "comprising", similar to the limitations such as, "including," "containing," or "characterized by," represent open-ended claim language and therefore, do not exclude additional, unrecited elements. See MPEP 2111.03 [R-1]. See *Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986)*; *In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981)*; *Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948)* ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts"). Therefore, the limitation "comprising", "comprises" or "includes" in the instant claims allows additional amino acid residues to be present on one or either side of the polypeptides; additional immunogenic polypeptides to be present on one or either side of the immunogenic portion and/or in between the two immunogenic polypeptides in the immunogenic portion. The open claim language in the claims also allows the fusion element (for example, MBP) to be present at the carboxy- or amino- terminal of the immunogenic portion, or at the carboxy- or amino- terminal of the whole fusion polypeptide. Since the unspecified generic limitation, 'a carboxy-terminal polypeptide', is not required to be a polypeptide present at the carboxy terminal of the whole fusion polypeptide, a reiterated Group A streptococcal M polypeptide being present at the carboxy terminal of the immunogenic portion meets the claim limitation. Because of these reasons, any prior art recombinant fusion polypeptide, as long as it comprises an immunogenic portion 'comprising' two reiterated immunogenic streptococcal M antigenic polypeptides each comprising at least 10 amino acids and a third identical or non-identical (i.e., non-reiterated) at least 10 amino acid-long immunogenic

streptococcal M antigenic polypeptide would meet the instant claims. See the rejection made below.

Mori *et al.* taught a recombinant MBP fusion product (i.e., fusion polypeptide), MBP-C region protein, comprising a recombinant immunogenic C region of Group A streptococcal type 12 M protein (see title; abstract; 'Methods' especially on pages 337 and 338; and first two paragraphs under 'Results'). The C region of the M protein 'comprises' at least two polypeptides that are at least 10 amino acids-long, for example: **Gly Leu Arg Arg Asp Leu Asp Ala Ser Arg Glu Ala Lys Lys** Gln Val Glu Lys Asp Leu Ala Asn Leu Thr Ala Glu Leu Asp Lys Val Lys Glu Glu Lys Gln Ile Ser Asp Ala Ser Arg Gln **Gly Leu Arg Arg Asp Leu Asp Ala Ser Arg Glu Ala Lys Lys** [Emphasis added] (see Figure 2A, especially the first five rows). The recombinant fusion protein is contained in PBS (i.e., a pharmaceutically acceptable diluent) (see paragraph bridging left and right columns on page 337). Given the open claim language used in the instant claims, the above-cited Mori's polypeptide comprising the set of amino acids (bold and non-bold sets) indicated above is viewed as the instantly recited immunogenic portion. The first set of 14 amino acids indicated above in bold letters and the middle set of 28 amino acid residues that are not shown in bold letters above meet the claim limitation: 'immunogenic portion wherein the immunogenic portion comprises at least two immunogenic polypeptides from Group A streptococcal M protein, the polypeptides comprising at least 10 amino acids". The last set of 14 amino acids indicated above in bold letters meets the limitation in part (b) of claims 12 and 15: "a carboxy-terminal polypeptide .... wherein the carboxy-terminal polypeptide is a reiteration of at least one immunogenic polypeptide from the amino terminal of the immunogenic portion". The immunogenicity or the capacity to elicit an immune response is considered as an inherent property of the prior art sets of polypeptides depicted above, since it is well known in the art that polypeptides 14 amino acids-long and 28 amino acids-long serve as immunogens and are capable of eliciting an immune response. That the above-depicted polypeptide comprised in Mori's recombinant fusion polypeptide serves intrinsically as a 'multivalent' immunogenic portion is also inherent from the teachings of Mori *et al.* in light of what was well known in the art at the time of the invention. For instance, Mori's 14 amino acid-long polypeptide from type 12 serotype of Group A streptococcus, **Gly Leu Arg Arg Asp Leu Asp Ala Ser Arg Glu Ala Lys Lys,** was also known to be comprised in the M protein antigen of another heterologous serotype of Group A streptococcus. Fischetti *et al.* or Vashishstha *et al.* disclosed the presence of

this identical 14 amino acid-long fragment also in the M protein of serotype 6 of Group A streptococcus (see Figure 7 of Fischetti *et al.* or Figure 1 of Vashishstha *et al.*). Therefore, the first set of **Gly Leu Arg Arg Asp Leu Asp Ala Ser Arg Glu Ala Lys Lys** and the middle set of 28 amino acid residues are viewed as the immunogenic polypeptides from serotype 12 M protein of Group A streptococcus and the second identical set of **Gly Leu Arg Arg Asp Leu Asp Ala Ser Arg Glu Ala Lys Lys** is viewed as representing an immunogenic polypeptide from serotype 6 M protein of Group A streptococcus. Thus, Mori's immunogenic portion inherently serves as a 'multivalent' immunogenic portion as recited.

Therefore, the disclosure of Mori *et al.* anticipates the instant claims. Fischetti *et al.* or Vashishstha *et al.* is **not** used as a secondary reference in combination with Mori *et al.*, but rather is used to show that every element of the claimed subject matter is disclosed by Mori *et al.* See *In re Samour* 197 USPQ 1 (CCPA 1978).

Claims 12, 15, 27 and 36 are anticipated by Mori *et al.*

Rejection(s) under 35 U.S.C. § 103

13) Claims 27, 30 and 31 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Mori *et al.* (*Pediatr. Res.* 39: 336-342, February 1996) and Dale *et al.* (WO 94/06421, already of record) ('421).

The teachings of Mori *et al.* are explained above, which do not disclose the use of an adjuvant, such as, Freund's adjuvant, along with their recombinant fusion polypeptide plus PBS diluent composition.

However, the addition of a Freund's adjuvant to a group A streptococcal recombinant hybrid M protein composition was conventionally practiced in the art at the time of the invention. For instance, Dale *et al.* ('421) taught the addition of complete or incomplete Freund's adjuvant to a group A streptococcal recombinant hybrid M polypeptide for the purpose of immunizing rabbits with the polypeptide (see page 11, second paragraph; page 36, third full paragraph; and page 37, first full paragraph).

It would have *prima facie* been obvious to one skilled in the art at the time the invention was made to add Dale's Freund's adjuvant to Mori's composition comprising the recombinant fusion polypeptide, to produce the composition of the instant invention with a reasonable expectation of

success, because Dale *et al.* taught it to be conventional and routine to add Freund's adjuvant to group A streptococcal recombinant hybrid M polypeptides. One of skill in the art would have been motivated to produce the instant invention for the expected benefit of effective immunization of rabbits since compositions with improved immunogenicity are ideally desired in the art.

Claims 27, 30 and 31 are *prima facie* obvious over the prior art of record.

14) Claims 27, 30, 32 and 34 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Mori *et al.* (*Pediatr. Res.* 39: 336-342, February 1996) in combination with Pillai *et al.* (US 5,334,379, already of record).

However, Pillai *et al.* disclose the adjuvant or immunomodulator activity of cytokines and lymphokines, such as, interferons, IL-2 and IL-4, and that IL-2 augments proliferation and differentiation of antigen or mitogen stimulated T cells. Cytokines and lymphokines are taught to have adjuvant activity with a capacity to enhance the immune response to an antigen (see column 1, lines 11-39). Pillai *et al.* further teach that cytokines and lymphokines "help evoke a protective immune response against marginally or non-immunogenic" unconjugated antigens (see paragraph bridging columns 6 and 7).

It would have *prima facie* been obvious to one skilled in the art at the time the invention was made to add Pillai's IL-2 or IL-4 to Mori's composition comprising the recombinant fusion polypeptide, to produce the composition of the instant invention with a reasonable expectation of success, because Pillai *et al.* explicitly teach that the recited cytokines have immune-enhancing adjuvant activity and the ability to evoke a protective immune response to the antigen present. One of skill in the art would have been motivated to produce the instant invention for the expected benefit of rendering Mori's composition immunogenic, since such compositions are ideally desired in the art.

Claims 27, 30, 32 and 34 are *prima facie* obvious over the prior art of record.

Relevant Prior Art

15) The prior art made of record and not currently relied upon in any rejection is considered pertinent to Applicants' disclosure:

- Fischetti *et al.* (*Science* 244: 1487-1490, 1989 - Applicant's IDS) taught that antigenic epitopes in the conserved region of the M protein are shared among >30 different M proteins (see page 1489). Fischetti *et al.* demonstrated homologous and heterologous protection in

mice immunized with a recombinant vaccinia virus construct expressing the conserved region of the structural gene encoding the VV:M6' upon challenge with homologous and heterologous group A streptococcal serotypes, including type M14 (see page 1490, first column).

Remarks

16) Claims 12, 15, 27, 30-32 and 36 stand rejected.

Claims 16, 17, 19, 21, 23, 34, 37, 38, 40, 42, 44 and 54-58 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

For clarity, it is suggested that Applicant replace the recitation "any one of claims 12 or 15-16" in claim 17 with --any one of claims 12, 15 and 16--. Analogous suggestion applies to claims 19, 21, 23, 32, 36-38, 40, 42 and 44. Similarly, it is suggested that Applicant replace the recitation "any one of claims 12 or 27" in claims 54, 56 and 58 with --any one of claims 12 and 27--.

17) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

18) Any inquiry concerning this communication or earlier communication(s) from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail service. The Examiner can normally be reached on Monday to Friday from 7.15 a.m to 4.15 p.m. except one day each bi-week which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

January, 2003

S. DEVI, PH.D.
PRIMARY EXAMINER